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Original Research Article

Clinical pharmacokinetics and pharmacodynamics of vildagliptin 50 mg sustained release tablet formulation in healthy Indian males after single and multiple-dose

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ABSTRACT

Background: Vildagliptin 50 mg once-daily is a clinically established anti-diabetic therapy in combination with a sulphonylurea and renally impaired patients. We developed sustained release (SR) vildagliptin 50 mg tablet formulation for prolongation of dipeptidyl peptidase-4 (DPP-4) inhibition coverage. The present study compares the pharmacokinetic (PK) and pharmacodynamic (PD) characteristics of investigational vildagliptin SR 50 mg tablet with Galvus® in healthy Indian adult males after single and multiple-dose administration.
Methods: Each randomized, open-label, two-period, cross-over study enrolled 36 healthy Indian adult male subjects for the assessment of single and multiple-dose PK/PD profiles of SR 50 mg vildagliptin under fed condition. The plasma drug concentrations were quantified using a validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) method. PK parameters (C_{max} (ng/ml), AUC0-18, AUC0-36, and AUC0-τ (ng.hr/ml), T_{max} (hour), t1/2 (hour), T_{maxss} (hour), $C_{\tau ss}$ (ng.hr/ml) were calculated using Phoenix® WinNonlin® software. The DPP-4 inhibition was determined in a fluorescence-based assay.
Results: Vildagliptin SR tablet showed prolonged PK/PD characters compared to Galvus®. All PK parameters expressed as Mean±SD. The single-dose PK measures were C_{max} (58.22±11.31), AUC0-18 (556.92±135.84), AUC0-36 (608.82±159.84), T_{max} (6.48±3.78). In the multiple-dose study, PK findings were C_{max} (73.20±17.71), AUC0-τ (714.36±303.21), $C_{\tau ss}$ (4.15±6.51), T_{maxss} (5.60±3.12). Vildagliptin SR 50 mg achieved prolonged DPP-4 inhibition (≥80%) for18-20 hours after single and multiple-dose administration as compared to Galvus® (12-13 hours).
Conclusions: Investigational vildagliptin SR tablet was found safe, well-tolerated after single and multiple-dose administration. Its extended DPP-4 inhibition profile compared to Galvus® may benefit the patient population on combination therapy with a sulphonylurea and renally impaired patients.

Keywords: OSMO, Sustained release, Pharmacodynamics, Pharmacokinetics, Vildagliptin

INTRODUCTION

Dipeptidyl peptidase-4 inhibitors (DPP-4i) introduced in 2006 as a new class of oral anti-diabetic drugs that stimulate insulin secretion by preserving endogenous incretin hormone, glucagon-like-peptide-1 (GLP-1) from degradation by DPP-4 enzyme. Thus far, the journey of DPP-4i in the clinical management of type-2 diabetes

(T2D) is exemplary due to their modest efficacy and favourable safety profiles. Moreover, they are weight neutral and do not cause hypoglycaemia. Resultantly, several DPP-4i are now available as an approved therapy.[1]

Among the most widely used DPP-4i, vildagliptin is the extensively studied agent; being used in more than 132 countries for the management of T2D.[2-4] This orally active, potent, small-molecule competitively and reversibly inhibits DPP-4 enzyme.[4] It is prescribed as monotherapy in patients with inadequately controlled glycaemia by diet and exercises alone or intolerant to metformin. It is also indicated as add-on therapy to patients that response insufficiently to other solo anti-diabetic therapies such as metformin, sulfonylureas, or thiazolidinediones. The recommended daily dose of vildagliptin is 100 mg, administered as 50 mg twice-daily. However, in the presence of a sulphonylurea, 50 mg once-daily dose is advised due to equal efficacy as twice-daily regimen and reduce risk of hypoglycaemia, weight gain.[5-7] Once-daily therapy is also recommended for patients with moderate to end-stage renal impairment.[5,6]

Vildagliptin single-dose is evident to produce maximal (≥80%) DPP-4 inhibition for 12 hours post-dose eliciting submaximal trough DPP-4 inhibition (approximately 25%) before next day dose.[8-10] Therefore, patients on 50 mg once-daily vildagliptin therapy deprived of prolonged DPP-4 inhibition. These facts alluded the scope for the development of SR formulation of vildagliptin to achieve extended DPP-4 inhibition compared to conventional immediate-release (IR) formulation of vildagliptin, Galvus®.

We explored the osmosis-mediated oral drug delivery (OSMO) approach for the development of a push-pull osmotic pump (PPOP) bi-layer SR vildagliptin 50 mg tablet formulation. Hence, the present study was conducted in healthy Indian male subjects to compare PK/PD characteristics of investigational SR 50 mg vildagliptin tablet with Galvus® after single and multiple-dose administration.

METHODS

A single and multiple-dose studies were conducted from November 2019 to January 2020 at Clinical Pharmacokinetics and Biopharmaceutics (CPB), Wockhardt Research Center, Aurangabad, India. The facility is approved by the Drugs Controller General of India (DCGI).

Subjects

Each, single and multiple-dose study planned to enrol 36 healthy Indian male subjects of 18-45 years age (both inclusive) with bodyweight≥50 kg, and a body mass index (BMI) ranging between 18.5 and 30.0 kg/m^2 (both inclusive). Subjects with normal findings on laboratory tests, physical examination, abdomen ultrasonography (USG), and serum amylase levels were recruited in the study. All participants asked to refrain from taking any over-the-counter or prescription medication two-weeks before initiation and during the study.

Standard exclusion criteria concerning blood donation, alcohol, drug addiction, caffeine intake, abnormal fasting and post-meal plasma glucose levels, difficulty in swallowing, and participation in other studies were applied. Subjects were also excluded if they had a prior history of allergy or hypersensitivity to vildagliptin, history of any psychiatric or metabolic disorder, impairment of renal, hepatic, cardiac, neurological, lungs or gastrointestinal function.

Study design

Each study was a single-centre, randomized, open-label, analyst-blind, two-treatment, two-period, two-sequence, and cross-over design; evaluating the PK, PD, and safety parameters of investigational vildagliptin SR 50 mg tablet (Wockhardt Limited, India; Batch No: NU10100; manufacturing date: 04-2019; expiry date: 03-2021) and marketed IR formulation, Galvus® (Novartis Pharma, Switzerland; lot no: JX1659; Manufacturing Date: 04-2019; Expiry Date: 03-2022) under fed condition. The primary objective of the study was so demonstrate the superiority of investigational SR vildagliptin formulation over IR formulation, Galvus® in terms of DPP-4 inhibition coverage.

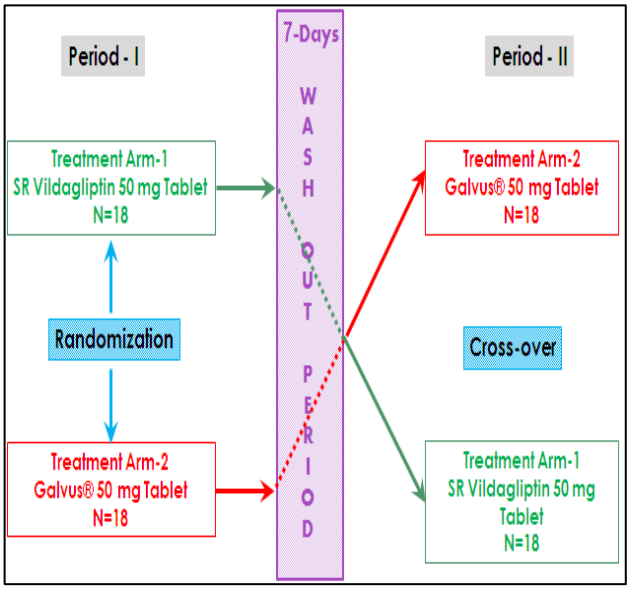

Figure 1: Single and multiple-dose study design for accessing PK/PD characters of SR vildagliptin tablet and Galvus®

Both studies comprised two-periods; each period recruited a total of 18 subjects to receive either

formulation treatment in a cross-over manner to expose a total of 36 participants for each treatment (Figure 1).

Each period separated by at least seven days of wash-out phase. All subjects housed at the study facility from a time adequate to ensure 10 hours overnight fasting before serving standardized test meal and further till 36 hours after drug administration in each period (for multiple-dose study, 36 hours after day-10 of treatment). The standardized test meal included high-fat, high-energy breakfast comprising two pieces of toast, two fried eggs, chicken (nuggets), potatoes, and 240 ml of whole milk. All participants served meals at- 10 hours (dinner), 4 hours (lunch), 8 hours (snacks), 12 hours (dinner), 24 hours (breakfast), 28 hours (lunch), 32 hours (snacks) and 36 hours (dinner) after drug dosing. All subjects received respective drug treatment in a sitting posture along with 240±02 ml of drinking water in each period, as a single tablet (single-dose study) or on each day from day-1 to day-10 (multiple-dose study). The time of drug administration for each subject recorded as the time at which the subject completed consumption of 240 ml of drinking water.

Pharmacokinetic evaluations

During each study, blood samples (3-5 ml) were collected from all participants via an indwelling intravenous catheter from the forearm vein. The blood samples kept in a cold water bath maintained at≤4°C during collection. Plasma was then isolated by centrifugation and stored at -80°C until analysis. For the quantification of vildagliptin concentrations, samples were extracted using solid-phase extraction technique (Oasis® HLB SPE Cartridge) on positive pressure unit and analysed by using a validated LC-MS/MS (AB Sciex API 3000 and Thermo Scientific TSQ Quantum) method.

In a single-dose study, a total of 23 blood samples were collected from each participant during each period at 0.00 hour (pre-dose) and at 0.50, 1.00, 1.50, 2.00, 2.50, 3.00, 3.50, 4.00, 4.50, 5.00, 6.00, 7.00, 8.00, 10.00, 12.00, 14.00, 16.00, 18.00, 20.00, 24.00, 30.00, 36.00 hours post-dose. The PK parameters were derived individually for each analysed subject from the plasma concentration-time profiles of vildagliptin SR and Galvus® 50 mg tablet using the non-compartmental model of Phoenix® WinNonlin® version 6.4 (Certara, Princeton, NJ, USA). The PK parameters calculated from the plasma concentration-time profile includes maximum concentration (C_{max}), the area under the plasma concentration-time curve (AUC) from zero to 18 and 36 hours concentrations (AUC_{0-18} and AUC_{0-36}), the time required to achieve maximal concentrations (T_{max}), and half-life ($t_{1/2}$).

In a multiple-dose study, a total of 26 blood samples were collected from each participant during each period at day-1, day-8, day-9 and day-10 as pre-dose samples (5 minutes before morning drug administration). On day-10 further blood samples were collected at 0.50, 1.00, 1.50, 2.00, 2.50, 3.00, 3.50, 4.00, 4.50, 5.00, 6.00, 7.00, 8.00, 10.00, 12.00, 14.00, 16.00, 18.00, 20.00, 24.00, 30.00 and 36.00 hours post-dose. All samples were handled and treated in the same manner as mentioned earlier in the single-dose study. An analytical method for the quantification of vildagliptin concentrations was not different from the single-dose study. The calculated PK parameters were AUC to the end of the dosing period ($AUC_{0-\tau}$), the maximum concentration at steady state (C_{maxss}), trough concentration ($C_{\tau ss}$), time to reach maximum plasma concentration at steady state (T_{maxss}), and half-life at steady state (T_{halfss}).

Pharmacodynamic evaluations

Plasma DPP-4 inhibition activity was determined in previously established fluorescence-based enzymatic assay method, utilizing Gly-Pro-7 amido-4-methylcoumarin hydrobromide (Sigma-Aldrich, MO, USA) as a substrate.[10,11] For the single-dose study, the DPP-4 inhibition was determined at 0.00 hour (pre-dose) and at 0.50, 1.00, 2.00, 4.00, 6.00, 8.00, 9.00, 10.00, 11.00, 12.00, 13.00, 14.00, 15.00, 16.00, 17.00, 18.00, 20.00, 22.00, 24.00, 30.00, 36.00 hours post-dose. For multiple-dose study, time-points for the DPP-4 inhibition were day-1, day-8, day-9 and day-10 (a total of 4 pre-dose) and 0.50, 1.00, 2.00, 4.00, 6.00, 8.00, 9.00, 10.00, 11.00, 12.00, 13.00, 14.00, 15.00, 16.00, 17.00, 18.00, 20.00, 22.00, 24.00, 30.00, 36.00 hours post-dose on Day-10. The calculated inter-assay and intra-assay percentage coefficient of variation (% CV) for the DPP-4 inhibition assay was 4.50 and 2.20, respectively.

Safety evaluations

Safety was assessed in all subjects from the screening period until the end of the study. A clinical examination including the recording of vital signs (sitting blood pressure, oral body temperature, respiratory rate and radial pulse rate) was performed at the time of screening, enrolment, and end of the study. Clinical laboratory tests (blood biochemistry and haematology) were performed for all participants at the time of screening and end of the study. Serum amylase test and abdomen USG was performed for all participants before check-in of period-I and post-study. Physical medical examinations were carried out at check-in and check-out of each period. All subjects were encouraged to report any sort of discomfort experienced during the study. Participants questioned for their well-being throughout the study.

Ethical standards

An ethical, scientific, and medical appropriateness of both the study protocols were reviewed by an independent ethics committee "The Aurangabad committee for Ethics Registered under DCGI, Government of India, New Delhi, India". Both the studies were conducted under the ethical principles originating in

the declaration of Helsinki and following the International conference on harmonization, good clinical practice guidelines, and applicable regulatory requirements and the study protocol. All subjects understood and signed the informed consent form to participate in the study. The study protocols were registered with DCGI as BENOC No. BE/SND/81/2019 (single-dose study) and BENOC No. BE/SND/80/2019 (multiple-dose study).

Statistical analysis

The values for weighted average DPP-4 inhibition [WAI (0-18 hours) and (0-24 hours)] calculated by dividing the AUC value for DPP-4 inhibition over 0-18 and 0-24 hours by 18 and 24, respectively. During each study, WAI at 0-18 and 0-24 hours were compared between the groups using unpaired t-test in GraphPad Prism 6 (GraphPad Software, San Diego, CA, USA).

RESULTS

Single-dose study endpoints

A total of 36 subjects were recruited in the study to receive a single bolus dose of either Galvus® 50 mg tablet or investigational vildagliptin SR 50 mg tablet under fed condition. Overall, of 36 subjects, 29 subjects completed both periods of the study successfully. Four subjects discontinued the study due to personal reasons, two subjects were withdrawn due to generalized body weakness and giddiness experienced during washout-period, and one subject was dropout from study due to failure of breath alcohol test during check-in of period-II. The average age, bodyweight and height of the study participants were 28.8 years, 62.83 kg, and 1.66 m, respectively. The baseline demographics and clinical baseline characteristics of the study participants are summarized in Table 1.

Table 1: Baseline demographic and clinical characteristics of participants in single-dose study.

Characteristic	Values	
	Range	Mean±SD
Age (years)	21-40	28.80±05.18
Weight (kg)	51.10-91.36	62.83±08.82
Height (m)	1.57-1.75	01.66±0.05
Body mass index (kg/m^2)	18.5-29.8	22.70±03.05
Fasting plasma glucose (mg/dl)	81.1-112.2	91.50±07.05
Post meal plasma glucose (mg/dl)	66.9-130.4	90.80±12.26

Data is expressed as mean±SD; N=36

Figure 2 depicts the plasma concentration profiles of both the formulations of vildagliptin after single-dose administration. All PK measures are expressed as mean±SD.

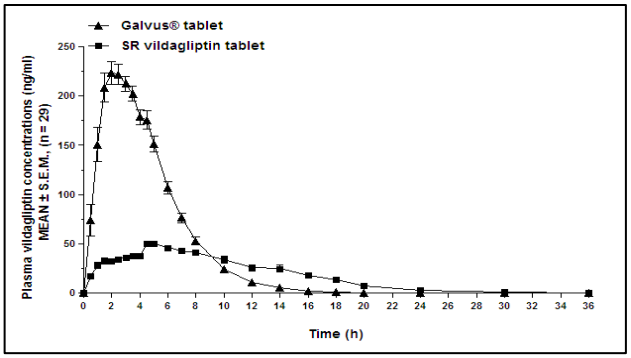

Figure 2: Plasma concentrations versus time profile of vildagliptin SR 50 mg tablet and Galvus® following their single oral dose.

All PK measures are expressed as mean±SD. Briefly, investigational vildagliptin SR exhibited low drug exposures than Galvus® as observed in C_{max} (58.22±11.31 versus 256.17±57.76), AUC0-18 (556.92±135.84 versus 1285.20±226.78) and AUC0-36 (608.82±159.84 versus 1286.40±227.19), respectively. However, median T_{max} and t1/2 of SR vildagliptin was found to be longer than Galvus® (5 versus 2.5 hours and 3.82 versus 1.72 hours, respectively). All PK parameters of vildagliptin SR were significantly ($p<0.0001$) different from Galvus® (Table 2).

Table 2: Single oral dose pharmacokinetics of investigational vildagliptin SR tablet and Galvus® in healthy Indian male subjects.

PK parameters		SR vildagliptin 50 mg tablet (N=29)	Galvus® 50 mg tablet (N=29)
C_{max} (ng/ml)	Range	33.23-88.86	146.29-385.00
	Mean±SD	58.22±11.31*	256.17±57.76
AUC_{0-18} (ng.hr/ml)	Range	298.88-813.57	817.88-1797.69
	Mean±SD	556.92±135.84*	1285.20±226.78
AUC_{0-36} (ng.hr/ml)	Range	332.01-949.60	820.97-1800.19
	Mean±SD	608.82±159.84*	1286.40±227.19
T_{max} (hours)	Range	1.00-16.00	1.00-5.00
	Mean±SD	6.48± 3.78*	2.55±1.12
	Median	5.00	2.50
$t_{1/2}$ (hours)	Range	1.55-20.04	1.36-3.46
	Mean±SD	5.04± 4.10*	1.86± 0.43
	Median	3.82	1.72

Data presented as Mean±SD; *p<0.0001vs Galvus® by unpaired t-test; Cmax, maximum plasma concentration; AUC0-18 and AUC0-36, area under plasma concentration-time curve from time 0 to the last sampling point; Tmax, time to reach Cmax; t1/2, terminal elimination half-life.

Figure 3 illustrates the DPP-4 inhibition profiles for both the formulations of vildagliptin after single-dose administration.

The vildagliptin SR 50 mg tablet exhibited maximal DPP-4 inhibition (≥80%) for 20 hours while Galvus® 50

mg showed ≥80% DPP-4 inhibition for 13 hours. The calculated weighted average DPP-4 inhibition [WAI (0-18 hours) and (0-24 hours)] was significantly different ($p<0.0001$) from one another between the groups (Table 3).

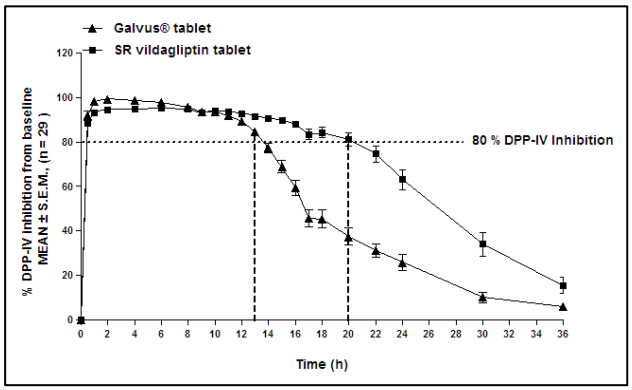

Figure 3: Comparative DPP-4 inhibition profiles of vildagliptin SR tablet and Galvus® after single-dose administration.

Table 3: Weighted average DPP-4 inhibition (WAI) at 0-18 and 0-24 hours.

Treatment arm	Single-dose study (N=29)		Multiple-dose study (N=34)	
	WAI (0-18 h)	WAI (0-24 h)	WAI (0-18 h)	WAI (0-24 h)
SR vildagliptin 50 mg tablet	91.0±0.6 ***	87.4±1.1 ***	88.2±1.6 ***	77.8±1.9 ***
Galvus® 50 mg tablet	85.1±1.0	72.5±1.5	74.4±1.2	60.6±1.3

Data presented as Mean±SEM; ***$p<0.0001$vs Galvus® by unpaired t-test

The calculated mean±SEM values for WAI (0-18 hours) and (0-24 hours) were 91.0±0.6, 87.4±1.1 with vildagliptin SR and 85.1±1.0, 72.5±1.5 with Galvus®, respectively. Both the formulations of vildagliptin were found safe and well-tolerated. Two cases of mild adverse events (body weakness and giddiness) were reported, which were believed to be not drug-related and were resolved.

Multiple-dose study endpoints

Out of 36 recruited healthy human volunteers, 34 participants completed both periods of the multiple-dose study successfully. One participant discontinued due to personal reason and another subject withdrawn from study due to protocol non-compliance.

Table 4: Baseline demographic and clinical characteristics of participants in multiple-dose study.

Characteristic	Values	
	Range	Mean±SD
Age (years)	18-38	26.70±05.47
Weight (kg)	52.08-84.10	65.65±09.72
Height (m)	1.60-1.81	01.69±0.04
Body mass index (kg/m^2)	18.5-29.5	22.88±03.30
Fasting plasma glucose (mg/dl)	74.1-107.7	90.60±06.05
Post meal plasma glucose (mg/dl)	68.2-123.9	92.70±13.45

Data presented as mean±SD; N=36

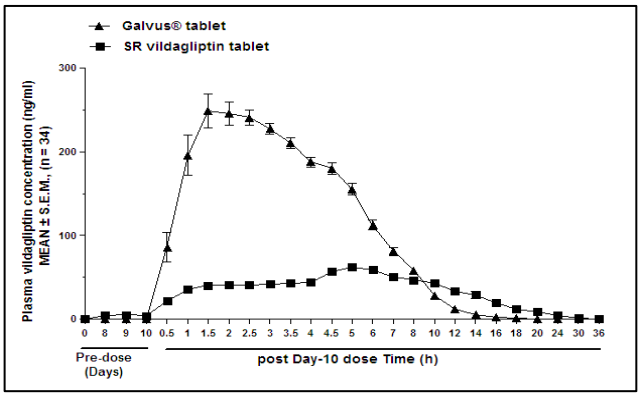

Figure 4: Plasma concentrations of vildagliptin SR tablet and Galvus® after multiple oral dosing (consecutive 10 days).

Figure 4 illustrates the plasma concentration profiles.

Table 5: Comparative pharmacokinetics of investigational vildagliptin SR 50 mg tablet and Galvus® post-10 days oral dosing in healthy Indian males (N=34).

PK parameters		SR vildagliptin 50 mg tablet	Galvus® 50 mg tablet
C_{maxs} (ng/ml)	Range	44.61-115.81	191.18-488.26
	Mean±SD	73.20±17.71*	304.40±78.78
$AUC_{0-\tau}$ (ng.hr/ml)	Range	220.76-1387.41	1032.01-1901.66
	Mean±SD	714.36±303.21*	1405.66±215.87
$C_{\tau ss}$(ng.hr/ml)	Range	0.00-31.20	0.00-2.29
	Mean±SD	4.15±6.51*	0.07±0.39
T_{maxs} (hr)	Range	0.50-14.00	0.50-5.00
	Mean±SD	5.60±3.12*	2.22±1.16
	Median	5.00	1.75
T_{halfss} (hr)	Range	1.28-16.13	1.24-3.21
	Mean±SD	3.91±2.96*	1.85±0.49
	Median	3.47	1.73

Data presented as Mean±SD; *$p<0.0001$ versus Galvus® by unpaired t-test; C_{maxss}, the concentration maximum at steady state; $AUC_{0-\tau}$, the area under the curve at steady state; $C_{\tau ss}$, the trough concentration; T_{maxss}, time to reach maximum plasma concentration at steady state; T_{halfss}, the half-life value at steady state.

Details of demographics and other baseline characteristics of the study participants are represented in Table 4. The mean values for age, bodyweight, and height of participants were 26.7 years, 65.5 kg, and 1.69 m, respectively. All subjects who completed study successfully were included in the safety assessment.

Table 5 represents the other calculated PK parameters of vildagliptin SR and Galvus® after their consecutive 10-days administration as a once-daily dose.

The PK measures after multiple-dosing of vildagliptin SR and Galvus® were, C_{maxss} (73.20±17.71 and 304.40±78.78), $AUC_{0-\tau}$ (714.36±303.21 and 1405.66±215.87), $C_{\tau ss}$ (4.15±6.51and 0.07±0.39), T_{maxss} (5.60±3.12 and 2.22±1.16) and T_{halfss} (3.91±2.96 and 1.85±0.49), respectively. All PK measures of vildagliptin SR tablet were found to be statistically ($p<0.0001$) different than Galvus®.

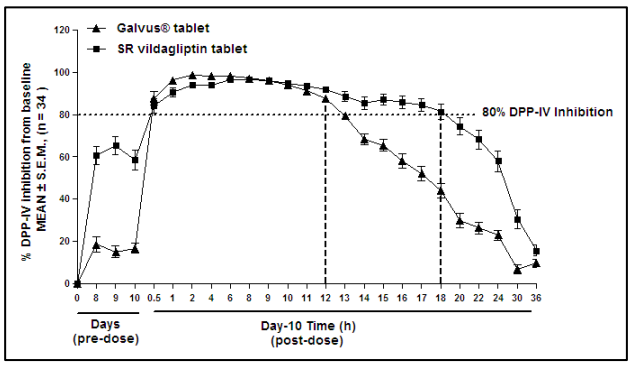

Figure: 5 Comparative DPP-4 inhibition profiles of vildagliptin SR and Galvus® following oral administration for 10 consecutive days.

Multiple-dosing of vildagliptin SR 50 mg resulted in prolonged maximal DPP-4 inhibition (≥80%) for 18 hours as compared to 12 hours with Galvus® on day-10 (Figure 5).

The current study reports a stable trough level of DPP-4 inhibition for both the formulations, assessed during the pre-dose phase (day-8, day-9 and day-10). However, a distinct difference in the levels of trough DPP-4 inhibition was observed during the pre-dose phase between both the formulations. The vildagliptin SR exhibited about 60% DPP-4 inhibition during pre-dose phase; whereas Galvus® showed approximately 20% DPP-4 inhibition. As expected, vildagliptin SR showed significantly ($p<0.0001$) higher WAI at 0-18 hours and 0-24 hours in comparison with Galvus®.

The calculated mean ± SEM WAI values for vildagliptin SR at 0-18 hours and 0-24 hours were 88.2±1.6, 77.80±1.9 and with Galvus® 74.4±1.2, 60.6±1.3, respectively (Table 3). Both the vildagliptin formulations were found to be safe and well-tolerated in the multiple-dose study.

No single adverse event reported in the study in either treatment arms.

DISCUSSION

Osmosis-mediated oral drug delivery is a voguish platform in controlled drug delivery. The technology offers zero-order drug release to furnish predictable, uniform therapeutic drug levels in circulation; producing a prolonged pharmacological effect.[12] Thus, vildagliptin SR formulation expected to elicit distinct PK profile with prolong DPP-4 inhibition than Galvus®.

In current study, single and multiple-dose administration of vildagliptin SR showed lesser C_{max}, C_{maxss}, AUC and longer T_{max}, $t_{1/2}$, T_{halfss} values than Galvus®. These PK differences attributed to effective and steady plasma concentrations plateau for longer interval. Therefore, vildagliptin SR produced less peak-to-through fluctuations compared to Galvus®. The observed difference in PK profiles of both vildagliptin tablets is due to their difference in formulation characters. Galvus® is an IR formulation; whereas vildagliptin SR is a PPOP bi-layer tablet formulation comprising pull and push layers that are made-up of swellable osmotic polymers such as polyethylene oxide (PEO N80 and PEO 303). The inner pull layer of the tablet holds 85% of an active drug, and outer film coating contains remaining 15% of active vildagliptin as an IR loading dose. As a result, the vildagliptin SR furnished active vildagliptin at sufficiently enough concentrations (about 10-15 times higher than IC50) for longer duration.

Single and multiple-dose vildagliptin SR administration elicited long plateau of steady drug concentrations ranging from 10 to 50 ng/ml. For vildagliptin, drug concentrations ranging from 10 to 15 ng/ml are reported sufficient to elicit nearly 80% DPP-4 inhibition.[9] Therefore, drug concentrations (10-50 ng/ml) achieved by vildagliptin SR were adequate to exhibit desired (≥80%) DPP-4 inhibition for 18-20 hours. Notably, stable but different levels of trough DPP-4 inhibition observed for vildagliptin SR (around 60%) and Galvus® (around 20%) during multiple-dose study at pre-dose phase on Day-8, 9 and 10. It may be due to the differences in their mean trough concentrations (4.15 versus 0.07 ng.hr/ml, respectively). The observed DPP-4 inhibition even at such lower drug concentrations may be due to high potency (IC50 about 3 nM), distinct DPP-4 inhibition mechanism and slow dissociation nature of vildagliptin. It acts as a surrogate substrate for DPP-4 and forms a reversible covalent enzyme-inhibitor complex. The binding kinetics at the catalytic site provides relatively slow dissociation. Thus, it exhibits persistent and extended DPP-4 inhibition despite short (approximately 3 hr) half-life.[13,14]

The current study did not measure the impact of extended DPP-4 inhibition of vildagliptin SR on GLP-1 and insulin levels which is a limitation of the study. However, a

clinically meaningful glycaemic control by gliptins is associated with at least≥80% DPP-4 inhibition, corresponding to augmentation of plasma GLP-1 levels by 2-3 folds.[15] Hence, longer plateau of effective drug levels and 80% DPP-4inhibition for 18-20 hours achieved by vildagliptin SR tablet is most likely to raise GLP-1 and insulin levels post-meal. In current study, the observed plasma concentration and DPP-4 inhibition profile of Galvus® after single and multiple-dose was similar to earlier reports.[8,9,16] Overall, observed differences in the PK parameters between vildagliptin SR and Galvus® correlates with their PD profiles.

Vildagliptin 50 mg once-daily regimen is a suitable add-on therapy for patient population that is insufficiently controlled by sulphonylurea monotherapy.[5-7,17] The sulphonylurea receptor-independent mechanism of vildagliptin makes it a favourable agent for combination with sulphonylurea class of drugs. This combination increases the glucose-sensitivity of both alpha and beta cells.[7,17] Prolonged DPP-4 inhibition in 50 mg once-daily regimen may leverage glycaemic control of this combination therapy. Vildagliptin 50 mg once-daily therapy is also recommended for patients with moderate, severe and end stage renal impairment.[5,6] Furtherance of glycaemic control due to extended DPP-4 inhibition may slower further renal damage in the patients with renal complications.

Initial studies by Novartis group reported 50 mg once-daily dose as clinically meaningful due to the optimal glycemic control after 12 and 24-weeks of treatment in T2D patients.[18,19] However, later study highlighted the ability of vildagliptin to elicit a dose-dependent efficacy in patients with higher Hb1Ac levels (>8%) due to the dominating contribution from nocturnal hepatic glucose production. The role of postprandial glycaemia is prominent in patients with relatively lower Hb1Ac; therefore, clinically significant efficacy with 50 mg once-daily regimen is possible. As this regimen produces desired DPP-4inhibition for 12 hours; covering the three meals during the day time.[19] On the ground of this available information, we speculate that prolonged optimum DPP-4 inhibition with SR formulation of vildagliptin may elicit clinically meaningful efficacy in T2D patient with moderate (≤8%) Hb1Ac. Indeed, a separate clinical study in T2D patients is needed to elucidate its potential as once-daily therapy.

CONCLUSION

The study achieved primary objective by demonstrating prolonged DPP-4 inhibition profile of vildagliptin SR 50 mg tablet compared to Galvus®. Its PD profile correlates with its distinct PK characteristics. Additionally, study reports vildagliptin SR as a safe and well-tolerable formulation after single and multiple-dose administration in healthy Indian adult males. The prolonged DPP-4 inhibitory property of vildagliptin SR may serve as a value addition to the existing glycaemic control of its combination therapy with a sulphonylurea. Moreover, T2D patients with renal complications may benefit from extended DPP-4 inhibition in vildagliptin SR 50 mg therapy.

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Ethical approval: All procedures performed in studies involving human participants were in accordance with Schedule Y (subsequent amendments) of CDSCO (Central Drugs Standard Control Organization), ICMR [Indian Council of Medical Research (2006)], ICH (The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use) E6 (R2) 'GCP' (Good Clinical Practice) (2016) and the Declaration of Helsinki (Brazil, October 2013). The study protocols were registered with DCGI as BENOC No. BE/SND/81/2019 (single-dose study) and BENOC No. BE/SND/80/2019 (multiple-dose study)

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